

AMENDMENTS TO THE CLAIMS

1. - 33. (Canceled)

34. (Previously Presented) An antibody or fragment thereof which is a modified antibody or modified fragment of an inhibitory antibody against FVIII, characterized in that the glycosylation of its variable region has been modified and in that it has substantially the same affinity to FVIII compared to the native antibody.

35. (Previously Presented) The antibody or fragment thereof according to claim 34, wherein said modification of the glycosylation is obtained by modulating the glycosylation of an antibody with a conserved N-glycosylation consensus pattern in its variable region.

36. (Previously Presented) The antibody or fragment thereof according to claim 34, wherein said modification of the glycosylation is obtained by modifying the amino acid sequence of the N-glycosylation consensus sequence in the variable region.

37. (Previously Presented) The antibody or fragment thereof according to claim 34, wherein said modification of the glycosylation is obtained by the introduction of a glycosylation consensus sequence in the variable region of the antibody.

38. (Previously Presented) The antibody or fragment thereof according to claim 34, wherein said inhibitory antibody against FVIII is Krix-1.

39. (Previously Presented) The antibody or fragment thereof according to claim 34, wherein the affinity of said antibody is lower than 1nM.

40. (Previously Presented) The antibody or fragment thereof according to claim 38, which is KRIX-1Q or KRIX-1A or an scFv fragment, Fab fragment or F(ab')₂ fragment of the monoclonal antibody KRIX-1Q or KRIX-1A.

41. (Currently Amended) The antibody or fragment thereof according to claim 38, wherein the scFv fragment is represented by SEQ ID NO: 26.

42. (Previously Presented) The antibody or fragment thereof according to claim 38, comprising an immunoglobulin heavy chain comprising an amino acid sequence having at least 90% sequence similarity to SEQ ID NO: 2.

43. (Currently Amended) The antibody or fragment thereof according to claim 38, comprising an immunoglobulin heavy chain comprising a sequence encoded by a nucleotide sequence having at least 90% sequence identity to SEQ ID NO: 1 ~~SEQ ID No 1~~.

44. (Currently Amended) The antibody or fragment thereof according to claim 38, comprising an immunoglobulin light chain comprising an amino acid sequence having at least 90% sequence similarity to SEQ ID NO: 4 ~~SEQ ID No 4~~.

45. (Currently Amended) The antibody or fragment thereof according to claim 38, comprising an immunoglobulin light chain comprising a sequence encoded by a nucleotide sequence having at least 90% sequence identity to SEQ ID NO: 3 ~~SEQ ID No 3~~.

46. (Withdrawn) A composition comprising a mixture of two or more antibodies or antibody fragments, said antibodies or antibody fragments being selected from the group

consisting of a native inhibitory antibody against FVIII or a fragment thereof and one or more modified antibodies or modified antibody fragments of said native antibody according to claim 34, wherein said mixture has an intermediate inhibitory activity against Factor VIII.

47. (Previously Presented) A pharmaceutical composition comprising the composition of claim 34.

48. (Withdrawn) A method for treatment and prevention of thromboembolic disorders, comprising administering an effective dose of a monoclonal antibody or fragment thereof according to claim 34.

49. (Withdrawn) The method for treatment and prevention of thromboembolic disorders according to claim 48, further comprising concomitantly administering drug(s) inhibiting platelet aggregation.

50. (Withdrawn) The method of claim 49, wherein said drug(s) inhibiting platelet aggregation, is(are) selected from the group consisting of asperin, abciximab (Rheopro^R) or an antithrombolytic agent.

51. (Withdrawn) A method for obtaining a library of at least two inhibitory antibodies against factor VIII with variable maximal inhibitory activity and with substantially the same affinity, said method comprising modifying the size of an inhibitory antibody against FVIII or fragment thereof by modifying the glycosylation in the variable region of said inhibitory antibody and selecting at least one antibody or fragment for which affinity is not substantially affected.

52. (Withdrawn) The method of claim 51, which method comprises the step of modifying the glycosylation in the variable region of an inhibitory antibody against FVIII or fragment thereof, and selecting those antibodies for which the affinity is not substantially affected.

53. (Withdrawn) The method according to claim 51, wherein said factor VIII inhibitory antibody is directed against the C1 domain of FVIII.

54. (Withdrawn) The method according to claim 51, wherein said factor VIII inhibitory antibody is Krix-1.

55. (Withdrawn) A library of factor VIII inhibitory antibodies obtained by the method according to claim 51.

56. (Withdrawn) The method according to claim 48, wherein said thromboembolic disorder is selected from the group consisting of deep vein thrombosis and pulmonary embolism secondary to surgical intervention, immobilization or chronic hereditary or acquired thrombophilia, and treatment of deep vein thrombosis, pulmonary embolism, stroke, atrial fibrillation, non Q wave myocardial infarct, non ST elevated myocardial infarct, unstable angina, sepsis or SIRS

57. (Withdrawn) A method for treatment and prevention of thromboembolic disorders, comprising administering an effective dose of the composition according to claim 46.

58. (New) The antibody or fragment thereof according to claim 34 comprising an immunoglobulin light chain sequence having at least 90% sequence similarity to SEQ ID NO: 4, and comprising an immunoglobulin heavy chain amino acid sequence having at least 90% sequence similarity to SEQ ID NO: 2, wherein the glycosylation site at positions Asn47 to Thr49 of SEQ ID NO: 2 is mutated.

59. (New) The antibody or fragment thereof according to claim 58, wherein said glycosylation site is mutated by changing Asn47 to Gln47, Asn47 to Glu47, Asn47 to Asp47, and/or by changing Thr49 to Ala49.

60. (New) The antibody or fragment thereof according to claim 59, wherein said glycosylation site is mutated by changing Asn47 to Gln47.

61. (New) The antibody or fragment thereof according to claim 34 comprising an immunoglobulin light chain sequence encoded by a nucleotide sequence having at least 90% sequence identity to SEQ ID NO: 3, and comprising an immunoglobulin heavy chain sequence encoded by a nucleotide sequence having at least 90% sequence identity to SEQ ID NO: 1, and wherein the glycosylation site at positions Asn47 to Thr49 encoded by SEQ ID NO: 1 is mutated.

62. (New) The antibody or fragment thereof according to claim 61, wherein said glycosylation site is mutated by changing Asn47 to Gln47, Asn47 to Glu47, Asn47 to Asp47, and/or by changing Thr49 to Ala49.

63. (New) The antibody or fragment thereof according to claim 62, wherein said glycosylation site is mutated by changing Asn47 to Gln47.

64. (New) The antibody or fragment thereof according to claim 34 comprising an immunoglobulin light chain comprising the CDR1, CDR2, and CDR3 sequences depicted in SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and comprising an immunoglobulin variable heavy chain comprising the CDR1, CDR2, and CDR3 sequences with SEQ ID NO: 33, SEQ ID NO: 34, and SEQ ID NO: 35, respectively, wherein the glycosylation site at positions 3 to 5 in the CDR1 of the immunoglobulin variable heavy chain comprising the sequence of SEQ ID NO: 33 is mutated.

65. (New) The antibody or fragment thereof according to claim 64, wherein the mutation is the change of Asn into Gln, Glu, or Asp at position 3 in the CDR1 of the immunoglobulin variable heavy chain comprising the sequence of SEQ ID NO: 33 and/or wherein the mutation is the change of Thr into Ala at position 5 in the CDR1 of the immunoglobulin variable heavy chain comprising the sequence of SEQ ID NO: 33.